REMARKS

Claims 61-111 are now pending in the application, with Claims 79-94 having been withdrawn and new Claims 95-111 now having been added. Claims 61-78 are rejected. Claims 61 and 64 have now been amended.

INTERVIEW

On November 6, 2007, a telephone interview was conducted between Applicants' representative, Mark S. Scott, and Examiner Chang-Yu Wang and SPE Christine Saoud. The rejections raised in the August 30, 2007 Final Office Action, the main cited references (Stoffel et al., Sutcliffe et al., and Yamada et al.) and proposed claim amendments were discussed. It was agreed that Applicants should, in their Response After Final, submit the page from the Stoffel et al. (Aug.) article showing the difference in amino acid sequence being reported by Stoffel et al., and that Applicants should present other evidence and arguments that distinguish Sutcliffe and Yamada. The Examiners also explained that the reason Sutcliffe was cited as a reference under 35 USC §102 was because the independent claims are written as "comprising" claims, and the Examiner did not prefer the use of the independent claim's exclusionary "wherein" clause, which states that the remaining PLP sequence (upstream of the PIRP-M sequence, SEQ ID NO:6) is absent from the fusion polypeptide.

The Examiners suggested moving this exclusionary element directly into the claim's definition of the PLP fragment amino acid sequence, and replacing the "absent" language with language stating that this sequence "lacks" the note upstream sequence. The Examiners agreed that, if the claims were clarified in such a way so as to exclude

the use of sequences having such upstream portions, the 102 rejection under Sutcliffe would be overcome.

Applicants' representative also specifically asked if it would be acceptable to retain a terminal exclusionary "wherein" clause at the end of the claim. The Examiners stated that they would be acceptable, as long as exclusionary language was present in the recitation of the PLP fragment's amino acid sequence, as described above.

The Examiners indicated that, if the claims were narrowed to recite that the fragment contains only SEQ ID NO:6 or at least residues 30-72 thereof, the rejections over both the Stoffel and Sutcliffe references and that the narrowed claims would likely be found allowable, although review of the actual claim amendments would be necessary before such a determination could be made. The Examiners also suggested that, if such narrowed claims were found allowable, then Applicants could consider pursuing a strategy of issuing such narrowed claims now, and then pursuing broader claim coverage, if supported by the Specification, in a later application. The Examiners also suggested that Applicants consider, if support exists, that the broader claim coverage could define native "mammalian" sequences that "correspond" to a native human sequence, and that have amino acid residues that "correspond" to residues of SEQ ID NO:6, using that sequence as a "reference sequence" to define the structural subject matter. The Examiners also suggested that Applicants could find help in this regard by reviewing patent documents by Kopchick in the field of human growth hormone, in order to seek to adapt Kopchick's use of "corresponding" language to the proposed amended claims, if appropriate support Applicants' Specification exists for that language.

CURRENT AMENDMENTS

Claim 61 has now been amended to simplify the recitation of the subject matter thereof by removing reference to mRNA, encoding functions, and IRES elements, and to instead define the claimed subject matter solely with reference to amino acid sequences. Specifically, Claim 61 has now been amended to recite that the proteolipid protein amino acid sequence present in the recombinant polypeptide molecule is that of a native mammalian or human proteolipid protein, to state that this sequence comprises the sequence of residues 30-72 of SEQ ID NO:6, and to further clarify that this sequence lacks the remainder of the amino acid sequence of the native protein that is located upstream (i.e. N-terminus-ward) of the SEQ ID NO:6-type portion thereof. Claim 61 has also now been amended to modify the "corresponding" language thereof. In specific, as per the Examiner's suggestion during the phone interview, Applicants have now reviewed a number of human growth factor-related patent documents by Kopchick and so have amended the present claims' "corresponding" language in accordance with the lessons learned from that review. Consequently, Claim 61 has now been amended to state that the native mammalian proteolipid protein is, or can be one that "corresponds" to, a human proteolipid protein, i.e. human PLP (SEQ ID NO:2 hereof) or human DM20 (SEQ ID NO:4 hereof). Also, in keeping with these lessons, Claim 61 has now been amended to state that the native mammalian protein has certain Met residues of or "corresponding" to the Met1 and Met30 residues of SEQ ID NO:6. Thus, SEQ ID NO:6 has been used as a reference sequence to further clarify the structure of

the proteolipid protein amino acid sequence present in the claimed recombinant polypeptide.

Support for the term "mammalian" is found, e.g., in original Claim 62 and at paragraphs [0045] and [0118] of the Specification hereof, numbered as per US Publ. No. 2006/0173168. Support for recitation of a mammalian protein that is homologous to (i.e. corresponds to) a human proteolipid protein is found, e.g., at paragraph [0118] of the Specification. Support for reference to Met1 and Met30 of SEQ ID NO:6 is found throughout the Specification and, particularly, in reference to the extensive description of and sequences presented for PIRP-M and PIRP-L, whose peptides begin with Met1 and Met30, respectively. Further support for the amendments to Claim 61 is found, e.g., in original Claims 1 and 61, and throughout the Specification.

Claim 64 has now been amended, and new Claim 95 has now been added, to define embodiments of the recombinant polypeptide in which amino acid sequence of the PLP "fragment" portion thereof consists of the amino acid sequence of residues 30-72 or 1-72 of SEQ ID NO:6, respectively. Support for these amendments is found in original Claims 1, 61, and 64, and throughout the Specification.

New Claim 96 has now been added to expressly define embodiments of the recombinant polypeptide in which the PLP fragment portion thereof is fused at its C-terminus to the fusion partner thereof. Support for Claim 96 is found, e.g., in original Claim 76 and throughout the Specification.

New Claim 97 has now been added to expressly define embodiments in which the recombinant polypeptide molecule is produced by expressing it from a recombinant nucleic acid. Support for Claim 97 is found, e.g., in paragraphs [0045]-[0053] of, and throughout, the Specification.

New Claims 98-111 have now been added to claim subject matter remaining from original Claims 61 ff., in light of the present amendments to those claims. Claims 61 ff. now recite that the PLP fragment portion of the recombinant polypeptide contains a native human or mammalian sequence having the sequence of residues 30-72 of SEQ ID NO:6. New Claims 98-111 recite that this PLP fragment portion contains a native mammalian sequence corresponding to the sequence of residues 30-72 of SEQ ID NO:6. Support for Claims 98-111 is founding original Claims 61, 63, 65-70, 73-74, 77-78, and 96, and as described for the above amendments.

The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein. The items raised in the Office Action are addressed below in the order in which they were presented.

MAINTAINED REJECTIONS UNDER 35 U.S.C. § 112

Claims 61-63, 66-70, 73-77 and 78 stand rejected under 35 U.S.C. § 112, first paragraph, for non-enablement and for insufficient written description, on the grounds that the claims encompass, as the PLP "fragment" sequence of the recombinant polypeptide, PLP fragments that begin with any mRNA IRES initiator Met codon, and thus encompass fragment sequences found throughout a PLP, or at least throughout

SEQ ID NO:6. Applicants believe this rejection may be a result of inadvertent unclarity in the wording of Claim 61 as originally presented. In order to clarify Claim 61, Applicants have now amended it to redefine the subject matter thereof in a manner that eliminates references to mRNA, IRES, and codons, and to instead simply define the sequence of the claimed recombinant polypeptide with reference to amino acid sequences. Applicants believe that the amended claim now more clearly defines (1) that the native PLP "fragment" portion in the recombinant polypeptide comprises a native human or mammalian PLP sequence that contains the sequence of residues 30-72 of SEQ ID NO:6, and (2) that the remainder of the native PLP sequence outside of that of or corresponding to SEQ ID NO:6 is excluded from the recombinant polypeptide. Applicants further believe that this more clearly defined scope is both sufficiently enabled and described by the Specification.

The claims as presently amended do not include fragment sequences found merely anywhere throughout a PLP, or at least anywhere throughout SEQ ID NO:6, and specifically do not include fragment sequences that begin with any internal amino acid residue of SEQ ID NO:6 or of residues 30-72 thereof. Applicants believe that these remarks and amendments overcome the rejections and respectfully request that they be withdrawn.

Applicants also note that these rejections state that PLP 215-232 (DM20 180-197), which is described by the below-discussed Yamada et al. reference as the active domain of a PLP peptide, corresponds to residues 45-62 of SEQ ID NO:6. However, Applicants point out that that the sequence of PLP residues 215-232 instead corresponds to that of residues 11-28 of SEQ ID NO:6. See the comparison box below.

PLP 215-232 (from page 8 of the present Application as published)

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Pro Gly Lys Val Cys Gly Ser Asn Leu Leu Ser Ile Cys Lys Thr Ala Glu Phe
215                 220                 225                 230
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DM20 180-197 (from page 10 of the present Application as published)

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Pro Gly Lys Val Cys Gly Ser Asn Leu Leu Ser Ile Cys Lys Thr Ala Glu Phe
180                 185                 190                 195
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SEQ ID NO:6 of the present Application

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          PLP 215-232                    aa 45-62 of SID6
mygvlpwnafpgkvcgsnllsicktaefqmtfhlfiaafvgaaatlvslltfmiaatynfavlklmgrgtkf
|         |         |         |         |         |         |         |
1         10        20        30        40        50        60        70
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This box shows that the sequence of PLP residues 215-232 is different from residues 45-62 of SEQ ID NO:6, and is a sequence entirely outside of residues 30-72 of SEQ ID NO:6, which is the reference sequence for all of the presently pending claims. Applicants' present response is made in light of that understanding.

In addition, Applicants believe that the rejections' references to aa **31**-72 of SEQ ID NO:6, may be a typographical error for residues **30**-72 of SEQ ID NO:6. Applicants' present response is made under that belief. However, if that belief is in error, then Applicants request further clarification from the Examiner as to the identity of that sequence.

MAINTAINED REJECTIONS UNDER 35 U.S.C. § 103

Claims 61-67, 69-78 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Stoffel et al. (*Hoppe-Seyler's Z. Physiol. Chem.* 363:1117-1131 (Sep. 1982)) in view of Metz et al. (*Somatic Cell & Mol. Genet.* 24:53-69 (1998)), Cha et al. (*Biotech. & Bioeng.* 67:555-74 (2000)), and Pryor et al. (*Protein Exp. & Purif.* 10:309-19 (1997)). The basis for the rejection appears to be (1) that Stoffel et al. describe preparation of "a 7.8 kDa polypeptide ... [that] corresponds to the 72 amino acid C-

terminal sequence..." (see Stoffel, p. 1117, column b), (2) the assertion that that 72-residue sequence is identical to SEQ ID NO:6 of the present Application.

Applicants initially note that the rejection states that Applicants, in their prior Response, argued that the 72-residue bovine lipophilin C-terminal sequence of Stoffel et al. is distinguished as an "expressed peptide" rather than part of the whole protein. There may be a misunderstanding of Applicants' remarks on this point. Applicants reaffirm and further clarify that Stoffel et al. (1) does not describe any 72-residue peptide as a naturally occurring molecule at all, (2) does not indicate that such a peptide has any biological activity or other use beyond providing sequence information about bovine lipophilin, and (3) does not describe a 72-residue peptide having the amino acid sequence of SEQ ID NO:6 of the present Application.

As to the first two points, Stoffel et al. artificially created their 7.8 kDa peptide from purified bovine lipophilin by a process involving (1) delipidation treatment, (2) reductive carboxymethylation to block Cys residues, (3) maleic anhydride treatment to block Lys residues, (4) cleavage at Arg-specific sites by trypsin, and (5) performic acid oxidation (see Stoffel pages 124 and 126 for a description of that process). They found the resulting derivatized fragment to be useful for extracting sequence information for part of a C-terminus-proximal portion of the bovine lipophilin macromolecule. But Stoffel et al. describe no biological activity of the derivatized fragment and present no apparent reason to one of ordinary skill in the art to select such a derivatized fragment for any purpose. In addition, the type of chemical processing employed appears to be such as to leave the peptide in a non-native state, containing chemical groups artificially introduced by that treatment, such as carboxymethyl residues. An artificially

carboxymethylated peptide would not be reasonably expected to exhibit the same biological activity as a native form of the peptide. Thus, even by reading Stoffel et al. in light of Yamada et al., one of ordinary skill in the art would not have found an apparent reason to select a peptide of Stoffel et al.

In regard to Applicants' third point, Stoffel et al. does describe a 72-residue amino acid sequence for the C-terminal 7.8 kDa fragment of bovine lipophilin, but this differs from SEQ ID NO:6. Although the rejection states that Stoffel's 72-residue peptide has an amino acid sequence identical to that of SEQ ID NO:6 of the present Application, Applicants have pointed out that Stoffel's sequence differs from that of SEQ ID NO:6 in Leu50Val.

Applicants note that the cited Stoffel reference (Stoffel (Sep. 1982)) does not describe the sequence of the bovine PLP portion containing their Val50. Instead, Stoffel et al. cite an earlier publication of their own work for that sequence. Specifically, Stoffel et al. cite a reference [2] for that sequence: see pages 1118 (col. a), 1128 (col. b), and 1130 (col. b), and the explanation at page 1124 (col. b) that the sequence determination thereof relies on cited reference [2]. In turn, cited reference [2] is Stoffel et al., *Hoppe-Seyler's Z. Physiol. Chem.* 363:855-864 (Aug. 1982). Stoffel (Aug. 1982) consistently sets forth the sequence of the relevant portion of the bovine PLP as having Leu50Val (see the sequences in both Fig. 3 and Fig. 4 at page 862 of that earlier reference). A copy of Stoffel (Aug. 1982) is attached to this Response: please see page 862 thereof. Thus, the two sequences are different.

In addition, the cited references provide no apparent reason for one of ordinary skill in the art to select the cited sequence of Stoffel et al. from among the various

available options, such as: the whole bovine lipophilin, the Trp IV fragment thereof, the CNBr III subfragment thereof, or any other fragment having a residue 215-232 functional domain sequence.

There is a further reason why one of ordinary skill in the art would not have selected a 72-residue, C-terminal amino acid sequence of a PLP protein. Yamada et al. does not suggest to select any PLP sequence containing a residue 215-232 functional domain sequence. Specifically, Yamada et al. report that they tested peptides containing PLP residues 215-232, as well as peptides having the sequence of PLP residues 209-217 or the sequence of PLP residues 264-276. Not only did the latter peptide have no effect, but the residue 209-217 peptide had a deleterious effect on cell proliferation (see Figure 6A at p. 2149 of Yamada et al.). Thus, one of ordinary skill in the art would read Yamada et al. to mean that the biological properties would be unpredictable for a peptide that contains both PLP residues 215-232 and additional PLP residues, such as are found in a 72-residue, C-terminal PLP sequence.

For the above reasons, Applicants respectfully submit that one of ordinary skill in the art would not have had an apparent reason to select a peptide of Stoffel et al. in order to routinely combine that peptide with a fusion partner, such as a GFP or His6 peptide of the Cha, Pryor, and/or Metz references. Therefore, Applicants respectfully submit that the subject matter as defined by the presently amended claims would not have been obvious to one of ordinary skill in the art from the cited references.

NEW GROUNDS OF REJECTION UNDER 35 U.S.C. § 102

Claims 61-66, 72-73, and 78 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Sutcliffe (US 5,242,798). The rejection states that Sutcliffe teaches recombinant polypeptides comprising a native PLP fragment fused to a fusion partner, and that Sutcliffe provides as an example of such a PLP fragment, SEQ ID NO:19 thereof, which is asserted as being identical to SEQ ID NO:6.

Applicants point out that the rejection quotes a portion of SEQ ID NO:7 from Sutcliffe (SEQ ID NO:7 is one of the 19 sequences described in Sutcliffe, but is not SEQ ID NO:19). This sequence is shown in Figure 7C-1 of Sutcliffe and contains 121 amino acid residues. The sequence search results shown at page 14 of the present Office Action note that this is "SEQ ID NO:7" and has "LENGTH: 121" and that it is only residues "50" to "121" thereof that are identical to the query sequence, i.e. SEQ ID NO:6 hereof.

Sutcliffe does not describe or suggest to use a smaller fragment of SEQ ID NO:7 thereof. Yet, all of the pending claims in the present Application define that the remainder of the PLP sequence, upstream of SEQ ID NO:6, are lacking from the claimed polypeptide. As a result, Applicants submit that Sutcliffe et al. does not provide all elements of the claimed subject matter. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

NEW GROUNDS OF REJECTION UNDER 35 U.S.C. § 103

Claims 61-78 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sutcliffe (US 5,242,798) in view of Metz et al. (*Somatic Cell & Mol. Genet.* 1998.

24:53-69), Cha et al. (*Biotech. & Bioeng.* 2000. 67:555-74), Pryor et al. (*Protein Exp. & Purif.* 1997. 10:309-19), and Huston et al. (*Int. Rev. Immunol.* 1993. 10:195-217). The rejection states that it would have been obvious to one of ordinary skill in the art to have selected the PLP fragment sequence of Sutcliffe, as described above, and to have routinely fused this to any one of the His-tag, GFP, or single chain Fv fusion partners described in Metz, Cha, Pryor, and Huston.

Applicants note that the present claims exclude use of PLP fragment portions have sequences extending beyond SEQ ID NO:6-type sequences. As discussed above, Sutcliffe et al. do not describe or suggest only SEQ ID NO:6 nor the selection of any other smaller portion of the 121 residue PLP fragment that is SEQ ID NO:7 of Sutcliffe et al. As a result, even if one of one of ordinary skill in the art had had some apparent reason to combine Sutcliffe with the addition references cited hereunder, that would not have provided all elements of the presently claimed subject matter. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Claims 61-78 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Stoffel et al. (*Hoppe-Seyler's Z. Physiol. Chem.* 1982. S. 1117-1131) in view of Metz et al. (*Somatic Cell & Mol. Genet.* 1998. 24:53-69), Cha et al. (*Biotech. & Bioeng.* 2000. 67:555-74), and Pryor et al. (*Protein Exp. & Purif.* 1997. 10:309-19) as applied to claims 61-67, 69-78, and further in view of Huston et al. (*Int. Rev. Immunol.* 1993. 10:195-217). The rejection states that it would have been obvious to one of ordinary skill in the art to have selected the PLP fragment sequence of Stoffel, as described

above, and to have routinely fused this to any one of the His-tag, GFP, or single chain Fv fusion partners described in Metz, Cha, Pryor, and Huston.

Applicants note that, as discussed above, one of ordinary skill in the art would have had no apparent reason to select a 72-residue bovine lipophilin fragment of Stoffel et al., even when Stoffel et al. is read in light of Yamada et al. Thus, there would have been no apparent reason to fuse such a Stoffel et al. fragment with any of the cited fusion partners. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

CONCLUSION

Applicants submit that a complete response has been made to the outstanding Office Action and that all of the stated grounds of rejection have been overcome thereby. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections and consider the present application to be in condition for allowance. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

Dated: 30 November 2005

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Enclosure
- Stoffel et al., *Hoppe-Seyler's Z. Physiol. Chem.* 363:855-864 (Aug. 1982).